REMARKS

Applicants have amended claims 1, 4, and 14-16. Applicants have also cancelled claims 17, 26, and 27 and added new claims 28 and 29. Accordingly, claims 1-16, 18-25, 28, and 29 are pending. No new matter has been added.

The Invention

The present invention relates, generally, to carboranyl-containing 5, 10, 15, 20-tetraphenylporphyrins having one or more of a variety of hydrophilic groups on the phenyl rings (see amended claim 1, formula 1). The invention particularly relates to such carboranyl-containing porphyrins having *at least four* carboranyl groups in combination with one or more of a variety of hydrophilic groups on the phenyl rings. The invention additionally relates to methods for using these porphyrin compounds in tumor imaging and diagnosis.

The advantage of the porphyrins of the present invention is multi-fold. Firstly, the at least four carboranyl groups provide more deliverable boron to the tumor target than porphyrin compounds containing fewer than four such carboranyl groups. Secondly, the high amount of boron in these compounds permits doses well below blood porphyrin toxicity thresholds. Thirdly, the one or more hydrophilic groups on the 5, 10, 15, and 20 porphyrin phenyl rings provides improved solubility properties. The improved solubility properties provides for improved administration (*i.e.*, less toxic solvents and solubilizers need be used) and better bioavailability (*i.e.*, effective selective delivery to the target along with low delivery to untargeted tissues).

Art Rejection Under 35 U.S.C. §102(b)

In the Office Action, the Examiner rejected claims 1 and 2 under 35 U.S.C. §102(b) for allegedly being anticipated by Frixa et al. (Org. Biomol. Chem., 1, 306-317 2003)). The Examiner specifically cites compounds 25, 26, 45, and 46 in Scheme 4 of Frixa et al. as anticipating the compounds represented by formula (1) in claims 1 and 2.

Claim 1 has been amended to require that at least four of Y^1, Y^2, Y^3, and Y^4 represent formula (2). Formula (2) is represented by the formula: $-X-(CR^1R^2)_r-Z$, wherein X is oxygen or sulfur, R^1 and R^2 are independently selected from hydrogen and C_1 to C_4 alkyl, r is 0 or an integer from 1 to 20, and Z is a carborane cluster comprising at least two carbon atoms and at least three boron atoms, or at least one carbon atom and at least five boron atoms, within a cage structure.

By the foregoing amendment, claim 1 requires that the structure corresponding to formula (1) have at least four carboranyl groups according to formula (2) and at least one hydrophilic group selected from groups W^1, W^2, W^3, and W^4. Both the carboranyl groups and the hydrophilic groups are bonded to one or more of the phenyl rings attached to the 5, 10, 15, and 20 positions of the porphyrin.

Support for the amendment to claim 1 is found in formula 1 on page 6 of the application; the porphyrin molecules exemplified in Examples 6 and 7 on pages 34-36 of the application; and the statements provided on page 19 in paragraph [0059] of the application.

In contrast to amended claim 1, Frixa et al. nowhere disclose, teach, or suggest a 5, 10, 15, 20-tetraphenyl porphyrin having at least four carboranyl groups and at least one hydrophilic group. For example, Frixa et al. teach a 5, 10, 15, 20-tetraphenyl porphyrin with the following substitutions with each substituent on a different phenyl ring: four carboranyl groups and no hydrophilic groups (see compound 23); three

carboranyl groups and one nitro group (see compound 24); two carboranyl groups and two nitro groups (see compounds 25 and 26); one carboranyl group and three nitro groups (see compound 27); and four nitro groups (see compound 28).

Accordingly, claims 1 and 2, as amended, cannot be said to be anticipated by Frixa et al.

Art Rejection Under 35 U.S.C. §103(a): Part A

The Examiner has rejected claims 1-13 under 35 U.S.C. 103(a) as allegedly being unpatentable in view of Miura et al. (US 5,877,165), Dolphin et al. (US 4,892,941), Bart et al. (US 2004/0023942 A1), and Frixa et al. (Org. Biomol. Chem., 1, 306-317 (2003)).

Specifically, the Examiner contends that Miura et al teach certain elements of the present invention, including Y, R, M relating to claim 1; the substituted positions relating to claims 2 and 5; and X, R^1 and R^2 relating to claims 7-13. The Examiner acknowledges that Miura et al. do not teach hydrophilic groups substituted on the phenyl ring.

The Examiner points to Dolphin et al. for teaching phenyl-substituted hydrophilic groups lacking in Miura (the Examiner cited columns 13-14, column 16, and claims 8-10 of Dolphin). The Examiner further points to Bart et al. for teaching the use of polyalkyleneoxide groups attached to the phenyl ring on a porphyrin structure (the Examiner cites formulas I and II of Bart). The Examiner refers to Frixa et al. for teaching, *inter alia*, a porphyrin compound that combines multiple carborane structures and hydrophilic groups on phenyl rings attached to the porphyrin.

One of the criteria for establishing a *prima facie* case of obviousness is that there must be some suggestion or motivation, as shown in the prior art, to combine reference teachings. In this regard, Applicants note that Miura et al., Dolphin et al.,

Bart et al., and Frixa et al., neither explicitly nor implicitly provide any suggestion or motivation for combining at least four carboranyl groups and at least one hydrophilic group onto the phenyl rings of a 5, 10, 15, 20-tetraphenyl porphyrin.

For example, none of the above references anywhere suggest that there would be any advantage in such a structure. Thus, the above references also do not provide motivation for considering, studying, synthesizing, or using compounds according to amended claim 1.

In contrast, claim 1 requires at least four carboranyl groups and at least one hydrophilic group be bonded onto the phenyl rings of the 5, 10, 15, 20-tetraphenyl porphyrin. Therefore, it cannot be said that a person having ordinary skill in the art would be motivated to combine the various cited references.

Another criterion for establishing a *prima facie* case of obviousness is that there must be a reasonable expectation of success in combining the reference teachings. However, none of the references cited above, individually or in combination, teach or suggest that it is possible to synthesize a porphyrin having at least four carboranyl groups and at least one hydrophilic group on the phenyl rings of a 5, 10, 15, 20-tetraphenylporphyrin molecule. In addition, none of the cited art would suggest that the synthesis of such a porphyrin compound is readily achievable, or possible.

In fact, as shown below, Frixa et al. teach away from an expectation of success for making a compound according to amended claim 1, *i.e.*, a compound having at least four carboranyl groups and at least one hydrophilic group on the phenyl rings of a 5, 10, 15, 20-tetraphenylporphyrin molecule.

Frixa's disclosed compounds contain a *total* of four groups selected from hydrophilic groups and carboranyl groups, each on a different phenyl group. Accordingly, a hydrophilic group is shown to be present *only if* such a hydrophilic

group takes the place of a carboranyl group. Thus, for example, Frixa et al. show that if four carboranyl groups are present, as in compound 23 of Frixa, then no hydrophilic group is included. Compound 27 of Frixa shows one hydrophilic group combined with three carboranyl groups. Compounds 25 and 26 of Frixa show two hydrophilic groups combined with two carboranyl groups. Lastly, Frixa et al. show that if four hydrophilic groups are present, as in compound 28, then no carboranyl group is included.

Since Frixa et al. show that a hydrophilic group is present only when taking the place of up to four carboranyl groups, Frixa et al. certainly does not provide any motivation for combining at least four carboranyl groups and at least one hydrophilic group. In fact, Frixa et al. can be interpreted as providing motivation for not combining at least four carboranyl groups and at least one hydrophilic group.

By contrast, claim 1 requires at least four carboranyl groups and at least one hydrophilic group be bonded onto the phenyl rings of the 5, 10, 15, 20-tetraphenyl porphyrin.

Applicants note that the last sentence in Part A of the Office Action, reference is made to "Curnow et al." without any further information. Since there is no listing in the list of cited references or in the Information Disclosure Statement that corresponds to this name, Applicants consider the reference to "Curnow et al." to be in error.

From the above, by combining Miura et al., Dolphin et al., Bart et al., and Frixa et al., it is evident that a person of ordinary skill in the art would not be provided a suggestion or motivating factor to combine the above references to result in the compounds of amended claim 1.

Accordingly, from the above it is evident that Miura et al., Dolphin et al., Bart et al., and Frixa et al. do not separately or in combination render claims 1-13, or any of the claimed invention, unpatentable.

Art Rejection Under 35 U.S.C. §103(a): Part B

The Examiner has also rejected the claims relating to methods for imaging tumors using the compounds of amended claim 1, *i.e.*, claims 14-17, under 35 U.S.C. 103(a). The Examiner has rejected claims 14-17 in view of Miura et al. (US 5,877,165) in further view of Dolphin et al. (US 4,892,941), Frixa et al. (Org. Biomol. Chem., 1, 306-317 (2003)), and Foye et al., (Principles of Medicinal Chemistry, Fourth Edition, Williams and Wilkins 1995).

Specifically, the Examiner points to Foye et al. for teaching that it is well known in the art to use porphyrins for imaging tumors (the Examiner specifically cites pp. 904-906 in Foye). The Examiner also points to Foye et al. as establishing that compounds of the porphyrin class are well known for use in imaging tumors due to their known accumulation within tumors.

Applicants have already shown above that Miura, Dolphin, and Frixa, alone or in combination, do not teach or suggest the compounds of the amended claims. In addition, rule 35 U.S.C. §103(b) provides that a biotechnological process claim is patentable when such a claim is directed to the use of a patentable claimed composition of matter. Rule 35 U.S.C. §103(b) has recently been broadened to include chemical processes. See 1184 OG 86 (March 26, 1996) and *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995).

Accordingly, since it has been demonstrated above that the claimed composition of the present invention is patentable, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection.

In addition to the above, Foye et al. do not teach or suggest imaging of tumors by use of carboranyl groups. In fact, Foye et al. do not even disclose the use of phenyl-derivatized porphyrins. In addition, as the Examiner mentioned on page 10 of the Office Action, Foye et al. do not teach single photon emission computed tomography, positron emission tomography, or magnetic resonance imaging.

Accordingly, though Foye et al. teach that porphyrins in general are applicable to tumor imaging, Foye et al. in combination with any of the other references noted above do not teach or suggest the methods according to amended claims 14-17. Nor do any of the foregoing references provide any suggestion or motivation that any porphyrin compounds even remotely similar to the compounds of the claimed invention could provide any of the advantages, as previously discussed above, for method claims 14-17.

Thus, from the above it is evident that Miura et al., Frixa et al., Dolphin et al., and Foye et al. do not separately or in combination render claims 14-17, or any of the claimed invention, unpatentable.

Art Rejection Under 35 U.S.C. §103(a): Part C

The Examiner has also rejected the claims relating to methods for bimodal cancer treatment, *i.e.*, claims 18-25, as being unpatentable under 35 U.S.C. 103(a). The Examiner has rejected claims 18-25 in view of Miura et al. (US 5,877,165), in further view of Frixa et al. (Org. Biomol. Chem., 1, 306-317 (2003)), in further view of Dolphin et al. (US 4,892,941), in further view of Foye et al., (Principles of Medicinal Chemistry, Fourth Edition, Williams and Wilkins 1995), and in further view of Patel et al. (WO 2004/030661 A2).

In particular, the Examiner recognizes that Foye et al. do not teach the compounds of the invention or the methods of boron neutron capture therapy, single

photon emission computed tomography, positron emission tomography, or magnetic resonance imaging.

The Examiner points to Patel, et al. for teaching the use of boronated compounds in the treatment of cancer. The Examiner points, in particular, to claims 15-21 of Patel.

Miura et al., Frixa et al., and Dolphin et al. have already been previously shown not to teach or suggest the compounds of the amended claims.

Foye et al. teach simply that tumors can be treated using porphyrin compounds (as the Examiner cited, pp. 904-906 of Foye). Foye et al. has already been shown above not to teach or suggest the use of any compounds remotely related to the compounds of the amended claims. Since method claims 18-25 include the compounds of amended claim 1, it is evident that Foye, alone or in combination with the other references above, nowhere teach or suggest a method of treating cancer according to the method of the present invention.

Patel et al. also do not teach or suggest the use of any compounds remotely similar to the compounds of the present invention in methods disclosed therein for treating cancer. For example, Patel et al. teach the use of two porphyrin compounds having very low water solubilities: CuTCPH and CuTCPBr (page 4, lines 11-28). CuTCPH is a 5, 10, 15, 20-tetraphenyl porphyrin containing four carboranyl groups and no hydrophilic groups (see Miura et al., U.S. 5,877,165, Figure 2 which shows similar NiTCPH compounds). CuTCPBr contains bromine instead of the H in CuTCPH, and thus, also does not contain any hydrophilic groups.

Patel et al. teach that the poor solubilities of CuTCPH and CuTCPBr present significant hindrances to using them for targeting tumors (page 4, line 20 to page 5, line 2). Patel et al. teach the inclusion of a polyhydroxy acid for improving the solubility of the porphyrin compounds (page 6, lines 20-27).

In stark contrast to Patel's method above, the present invention teaches the use of porphyrin compounds whose solubility properties are optimized not solely by combining them with hydrophilic substances, as in Patel, but by the incorporation of at least one hydrophilic group onto the porphyrin compound of the invention. Therefore, Patel et al., alone or in combination with the other cited references, nowhere teach or suggest, or show any motivation for, the methods relating to claims 18-25 of the present invention.

Accordingly, from the above it is evident that Miura et al., Frixa et al., Dolphin et al., Foye et al., and Patel et al. do not separately or in combination render claims 18-25, or any of the claimed invention, unpatentable.

In addition, in view of 35 U.S.C. §103(b), as mentioned above for the 103(a) rejection of the method claims directed to tumor imaging, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection of these method claims as well.

Formality Rejections

The Examiner rejected claim 4 under 35 U.S.C. 112, second paragraph. Claim 4 was rejected for alleged indefiniteness in the use of the limitation -X-$(CR^1R^2)_r$-Z (2). The Examiner interpreted the "(2)" in the limitation as referring to two "Z" variables.

Applicants wish to point out that the "(2)" noted by the Examiner functions as a reference to formula (2) and is not a subscript designating 2 "Z" variables. For support, Applicants refer to page 5, line 8 of the application. Applicants also refer to claim 1 for support.

However, Applicants observe that, by some irregular typesetting in claim 4, the "(2)" appears to be slightly below the corresponding limitation, and thus, may be misinterpreted. Accordingly, Applicants have amended claim 4 by moving the "(2)" more in line with the corresponding limitation. Since claims 5-13 are dependent on

claim 4, these claims are thereby accordingly corrected. Applicants consider the foregoing amendment to properly address the Examiner's concerns.

The Examiner has also rejected method claims 14, 15, and 16 under 35 U.S.C. 112, second paragraph. The Examiner considers the claims incomplete for omitting essential steps. The Examiner suggests that inclusion of the subject matter of claim 17 into the foregoing method claims would overcome the presumed deficiencies.

Applicants have amended independent claims 14-16 by including into them the subject matter of claim 17. Accordingly, claim 17 has been cancelled. Applicants consider the foregoing amendment to properly address the Examiner's concerns regarding claims 14-16.

Claim Objections

The Examiner suggests that claim 26 would be allowable if written in independent form with all of the limitations of the base claim. Accordingly, Applicants have cancelled claim 26 and included new claim 28 to replace claim 26. New claim 28 contains all of the limitations of claim 26 and the base claim, and is in independent form.

The Examiner also objected to claim 27, which depends from claim 26, as being improper in form. In particular, the Examiner considers the claim to be a multiple dependent claim in improper form. However, Applicants never intended for claim 27 to be a multiple dependent claim. Accordingly, to clarify the subject matter of claim 27, Applicants have cancelled claim 27 and included new claim 29 to replace claim 27. New claim 29 is dependent on new claim 28. Support for new claim 29 is found in paragraphs [0042] and [0043] of the application.

In view of the above amendments and remarks, allowance of pending claims 1-16, 18-25, 28, and 29 is earnestly requested. If the examiner has any questions

concerning this application, it is respectfully requested that the examiner contact applicants' agent at the telephone number provided below.

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